PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gerhard SCHMAUS, *et al.*	Confirmation: **1516**
Appln. No.: **10/502,132**	Examiner: **Yong Soo CHONG**
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Attorney Docket No.: **3968-120**	Customer No.: **30448**

For: **SYNERGISTIC MIXTURES OF 1-2, ALKANE DIOLS**

DECLARATION OF CO-INVENTOR DR. GERHARD SCHMAUS
UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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I, Dr. Gerhard Schmaus, a citizen of Germany, residing at Herrenburgstraße 29, 37671 Höxter-Bosseborn, Germany, declare as follows:

1. I hold a "Dr. rer. nat." in biology which I obtained in 1988 at the University of Würzbug in Germany. Since 1988, I have been employed by Dragoco GmbH and Co. KG ("Dragoco") and its successor in interest, Symrise GmbH and Co. KG ("Symrise"). Symrise is the assignee of the '132 Application.

From 1988 until 1999, I investigated new natural and synthetic flavor and fragrance materials. Since 2000, I have been entrusted with research and development of antimicrobial agents particularly those useful in product preservation of cosmetics, such as deodorants, anti-acne agents and anti-dandruff agents. My activities as a pharmaceutical biologist during the last 20 years are characterized by several highlights, and for some of these highlights

Symrise or its predecessor, Dragoco, decided to apply for national and/or international patents, in the field of cosmetic research, for example US 7,119,123, US 7,247,295, US 2006/0089413, US 2007/0054967, US 2007/0098655, US 2007/0265352, US 2007/0059331, WO 01/66097, WO 01/85120, WO 2006/134013, WO 2007/062957, WO 2007/077260, WO 2008/046791, WO 2008/046796 and WO 2008/047695.

2. I am a co-inventor for the U.S. Patent Application No. 10/502,132 entitled "Synergistic Mixtures of 1,2-Alkane Diols" (hereafter the '132 Application), and the subject matter described therein. Accordingly, I am familiar with the subject matter described in the '132 Application.

3. I have reviewed the '132 application, the Office Action mailed March 10, 2008 and references cited therein.

4. In the Office Action mailed March 10, 2008 (hereinafter "Office Action"), claims 1-5, 7 and 9-21 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent Application Publication No. 2001/0036964 by Clarkson, *et al.* (hereinafter "Clarkson") in view of U.S. Patent No. 5,670,160 issued to Eggensperger *et al.* (hereinafter "Eggensperger"), U.S. Patent Application Publication No. 2003/0100613 by Riebel *et al.* (hereinafter "Riebel"), and U.S. Patent Application Publication No. 2002/00998211 by Cupferman *et al.* (hereinafter "Cupferman").

The amended claims are drawn to compositions containing a mixture of 1,2-alkanediols that exhibit an antimicrobial effect characterized by a Kull value of less than 1. For example, amended claim 1 recites:

> Claim 1. (currently amended) An antimicrobial composition, comprising an antimicrobial effective amount of a mixture of ~~two, three or more straight chain~~ 1,2-alkanediols [[,]] consisting of two or more straight chain 1,2-alkanediols having ~~the~~ chain lengths that ~~of which~~ (i) are different and (ii) ~~in each case~~ are in the range of 5 to 10 C atoms, wherein said mixture of 1,2 alkandiols exhibits an antimicrobial effect characterized by ~~effective amount is~~

~~that amount which results in~~ a Kull value of less than 1 ~~for the antimicrobial effect exhibited by said mixture of 1,2-alkanediols~~.

The claim has been amended to clarify that the phrase "mixture of 1,2-alkanediols" refers only to straight chain 1,2-alkanediols that are (i) different, and (ii) in the range of 5 to 10 carbons long. The claims clearly state that the mixture of 1,2-alkanediols, which has been defined to exclude preservatives or other biocides, exhibits an antimicrobial effect characterize by a Kull value of less than 1. In other words, the mixture of 1,2-alkanediols exhibits a synergy with respect to the individual 1,2-alkanediols that constitute the mixture of 1,2-alkanediols.

According to the Office Action, Clarkson discloses individual 1,2-alkanediols, but fails to disclose "a composition comprising the particular combination of alkyldiols [claimed] herein or the specific preservatives such a 1,2-dibromo-2,4-dicyanobutane, 2-phenoxyethanol, and 3-iodo-2-propinyl-butyl carbamate." The Office Action asserts that the combination of Eggensperger and Riebel disclose each of the three specific preservatives. It is asserted that Cupferman discloses a composition with a synergistic antimicrobial action that contains at least one polyol in combination with 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one or sodium capryl lactyl lactylate.

It is well known that the fields of chemistry and biology are unpredictable arts. The current invention deals with an unexpected results, *i.e.*, synergistic antimicrobial activity, that is the result of chemical interactions with a biological organism. To this day, me and my colleagues have not identified the mechanism that causes the synergistic antimicrobial efficacy of the claimed mixtures of 1,2-alkanediols. Thus, even in hindsight, more than six and a half years after the filing of the German priority application (DE102 06 759.7. filed 02-19-2002), the claimed result is still not explained and could not be predicted using a model.

Of the four references cited in the rejection of claims 1-5, 7 and 9-21, only one of the references, Cupferman, even arguably discloses a synergistic antimicrobial effect for any mixture of compounds. Thus, the only reference that could possibly disclose or suggest the claimed synergistic antimicrobial effect is Cupferman.

Synergy in the biological and chemical arts is very valuable because many chemicals used in these areas are very expensive ingredients. Thus, extensive research is conducted to identify synergistic combinations that can reduce the amounts of such ingredients that must be added while achieving a desired antimicrobial effect. Even with all of this research, it is difficult to determine where a synergistic antimicrobial effect may arise, because the mechanism behind the synergy of chemicals as they interact with biological organisms or constituents are poorly understood.

That said, it is sometimes possible to guess that where there is a synergy between two molecules, another molecule closely related to one of the molecules (such as an isomer or stereoisomer) may be substituted to produce a similar synergistic effect. With that in mind, we can consider 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one and sodium capryl lactyl lactylate, which Cupferman discloses as producing a synergistic antimicrobial effect when combined with 1,2-alkanediols.

2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one is an aromatic seven carbon ring formed from three double bonds and a ketone group. There is simply nothing in the biological or chemical arts that would suggest that 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one and a first straight chain 1,2-alkanediol with 5 to 10 carbon atoms would behave similarly with respect to producing a synergistic antimicrobial effect when combined with a second straight chain 1,2-alkanediol with 5 to 10 carbon atoms. Thus, there is no reason to expect that a synergistic antimicrobial effect would be produced when the 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one in Cupferman is substituted with a 5 to 10 carbon straight chain 1,2-alkandiol.

Sodium capryl lactyl lactylate is the sodium salt of the caprylic ester of lactyl lactate. There is simply nothing in the biological or chemical arts that would suggest that Sodium capryl lactyl lactylate and a straight chain 1,2-alkanediol with 5 to 10 carbon atoms would behave similarly with respect to producing a synergistic antimicrobial effect when combined with a different straight chain 1,2-alkanediol with 5 to 10 carbon atoms. Thus, there is no reason to expect that a synergistic antimicrobial effect would be produced when the sodium

capryl lactyl lactylate in Cupferman is substituted with a 5 to 10 carbon straight chain 1,2-alkanediol.

It is highly noteworthy that Cupferman was seeking to identify a synergistic antimicrobial effect using 1,2-alkanediols, but did not discover that specific mixtures of 1,2-alkanediols, such as those claimed, produce a synergistic antimicrobial effect. However, perhaps the strongest evidence against the attempt to make the substitution required to support the Examiner's assertion of obviousness is that none of the references attempt to generalize a class of compounds that will exhibit a synergy when combined with a 1,2-alkanediol. Clearly, if the claimed invention were obvious, and substitutions producing synergies simple, Cupferman would have identified that a mixture of at least two different straight chain 1,2-alkandiols with 5 to 10 carbon atoms exhibited a synergistic antimicrobial effect.

The remaining references are only tangentially related to the claimed subject matter. The Office Action asserts that Clarkson discloses individual 1,2-alkanediols, but fails to disclose "a composition comprising the particular combination of alkyldiols [claimed] herein or the specific preservatives such a 1,2-dibromo-2,4-dicyanobutane, 2-phenoxyethanol, and 3-iodo-2-propinyl-butyl carbamate." Thus, Clarkson merely stands for the proposition that 1,2-alkanediols can be mixed with other ingredients. This does nothing to disclose or suggest the claimed synergistic antimicrobial action produced by the mixture of two different straight chain 1,2-alkanediols with 5 to 10 carbons.

The Office Action asserts that the combination of Eggensperger and Riebel disclose each of the three specific preservatives. This merely discloses that these ingredients exist, but does nothing to disclose or suggest using them in combination with the claimed mixture of two or more different straight chain 1,2-alkanediols with 5 to 10 carbons, where the mixture of 1,2-alkanediols exhibits a synergistic antimicrobial action.

For the reasons outlined above, the only possible conclusion is that nothing present in Cupferman or any other cited reference, whether alone or in combination, would disclose or suggest that the claimed mixture of 1,2-alkanediols would exhibit a synergistic antimicrobial effect as established by Kull values. Accordingly, the combination of Clarkson,

Eggensperger, Riebel, and Cupferman fails to establish that the subject matter of the claims is obvious.

5. In the Office Action, claim 8 is rejected under 35 U.S.C. 103(a) as being obvious over French Patent No. 2 747 572 issued to Greff (hereinafter "Greff"). The Office Action asserts that Greff is directed to a composition consisting of two or more straight chain 1,2-alkanediols, wherein the chain length is different and in the range of 5 to 10 carbon atoms. The Office Action acknowledges that "Greff fail[s] to disclose a specific combination of two alkane-diols with a linear chain between 5 to 10 carbons."

Similar to the discussion of Clarkson, Eggensperger, Riebel, and Cupferman found above, there is simply nothing in Greff that discloses or suggests that the use of two different straight chain 1,2-alkanediols with 5 to 10 carbons would exhibit a synergistic effect. Claim 3 of Greff is drawn to the compositions of claims 1 and 2 along with glyceryl poly(meth)acrylate. A review of claims 1 and 2 indicates that they recite "the alkane-diol is octane-1,2-diol." Thus, claim 3 discloses that a mixture of a linear or branched alkanediol, preferable octane-1,2-diol, and glyceryl poly(meth)acrylate produces an unmeasured synergistic effect of two mechanisms (presumably the two compounds).

There is nothing structurally similar (*e.g.*, isomer, stereoisomer, etc.) about a straight chain 1,2-alkanediol with 5 to 10 carbons and glyceryl poly(meth)acrylate to suggest that there would be a synergy between two 1,2-alkanediols. Specifically, there is simply nothing in the biological or chemical arts that would suggest that glyceryl poly(meth)acrylate and a straight chain 1,2-alkanediol with 5 to 10 carbon atoms would behave similarly with respect to producing a synergistic antimicrobial effect when combined with a different straight chain 1,2-alkanediol with 5 to 10 carbon atoms. Thus, there is no reason to expect that a synergistic antimicrobial effect would be produced when the glyceryl poly(meth)acrylate in Greff is substituted with a 5 to 10 carbon straight chain 1,2-alkandiol.

Clearly, if there were such a suggestion, Greff, who was looking for synergies, would have sought patent protection for it. For the reasons outlined above, it is clear that there is nothing present in Greff of any other cited reference, whether alone or in combination, that

would disclose or suggest the claimed mixture of 1,2-alkanediols would exhibit a synergistic antimicrobial effect as established by Kull values.

6. In the Office Action, the Examiner asserts that the unexpected results provided in the Specification do not overcome the obviousness rejection. The Examiner asserts that:

> the results in the specification are not commensurate with the scope of the instant claims. It is noted that the instant claims do not recite any limitation on the amounts of the 1,2-alkanediols. Applicant's specification only show[s] data for the following amounts: 0.25%, 0.5%, 1%, 2% and 3% for the disclosed 1,2-alkandiols. This is not enough to support the entire range of up to 100% as claimed.

Office Action, page 8.

I would respectfully submit that this demonstrates a clear misunderstanding of the claims, which the current amendment should clarify. The Kull value calculation is based on the minimum inhibitory concentration (MIC), which is dependent on the ***ratio*** of the various 1,2-alkanediols in the mixture of 1,2-alkanediols. However, the MIC is independent of the ***amount*** of 1,2-alkanediol mixture in the composition. Thus, the objection to the data found in the Office Action is simply not relevant to the claimed subject matter.

The methodology used to determine the MIC value of individual 1,2-alkanediols and mixtures of 1,2-alkanediols can be found in the specification, *see* paragraphs [0101]-[0118]. In addition, the equation used to calculate the Kull value can be found in Table 4, *see* Specification, p. 33.

When the mixture of 1,2-alkanediols is added to an antimicrobial composition, the amount added does not impact the Kull value, which is determined based on the ratio of the 1,2-alkanediols. This derivation of Kull value is a measure of synergy that is well accepted by those of ordinary skill in the art of antimicrobial sciences. Furthermore, a person of ordinary skill in the art would not add more than the MIC for the target microbe

because adding more than this amount would increase costs and could raise issues with safety. Accordingly, the Examiner's objection to Applicant's data is unfounded.

7. In order to demonstrate that a synergy is not necessarily present for mixtures of 1,2-alkanediols consisting of two or more 1,2-alkanediols, I have conducted experiments to determine the Kull values for mixtures of 1,2-hexanediol and 1,2-octanediol, having different ratios thereof, for their activity against *Staphylococcus aureus* (ATCC 6538).

1,2-Hexanediol (C6), 1,2-octanediol (C8) and mixtures having different weight ratios of 1,2-hexanediol (C6) and 1,2-octanediol (C8) were prepared and their activity against *Staphylococcus aureus* (ATCC 6538) was measured in accordance with the following protocol used to determine the minimum inhibiting concentration (MIC). The MIC values were used to calculate Kull values in order to evaluate whether a synergy was present for each ratio of 1,2-hexanediol and 1,2-octanediol.

Test conditions for MIC measurements:

Test conditions were consistent with the procedures set forth in Example 2 of the Specification, paragraphs [0101]-[0118]. The antimicrobial action of 1,2-alkanediols and of 1,2-alkanediol mixtures according to the invention was demonstrated with the aid of the agar dilution method based on DIN 58 940/ICS and DIN 58 944/ICS. Petri dishes 5.5 cm in diameter were charged with 4.5 ml freshly prepared Mueller-Hinton agar (Merck, Ref. 1.05437), to which the various concentrations of the diluted samples were added in 10% (V/V) = 0.5 ml. Stock solutions: 5ml of the pure samples were diluted in 5 ml distilled water (500,000 ppm/ml). The further test concentrations of the particular dilution series, which were prepared in the form of geometric series, were prepared by progressive 1:1 dilution of 2.5 ml of stock solution with 2.5 ml distilled water. By means of a further dilution with the test agar (0.5 ml sample or corresponding dilutions + 4.5 ml agar), 10 times lower final concentrations were achieved in each case (corresponds to an initial concentration of 50,000

ppm in each case). Two agar plates were poured per test concentration and nutrient medium. The following controls were carried out, with two agar plates in each case

K1: 5.0 ml Mueller-Hinton agar	(not inoculated)
K2: 4.5 ml Mueller-Hinton agar + 1.5 ml distilled water	(inoculated)
K3: 4.5 ml Mueller-Hinton agar + 1.5 ml distilled water	(inoculated)
K4: 5.0 ml Mueller-Hinton agar	(inoculated)

After solidification and drying (approx. 1 h at 36° C.), the test plates were inoculated in point form with, in each case, 1 µl of the test germ suspension. To check purity and identity, test germ was grown aerobically on Caso-Agar (BioMérieux, Ref. 43555).

Test Germ	Strain Name	CFU*/ml
Staphylococcus aureus	ATCC6538	2.6×10^7

(CFU* = colony-forming units)

The preparation of the test germ suspensions of *Staphylococcus aureus* that grew aerobically was carried out by incubation of Mueller-Hinton broth (Merck, Ref. 1.10293) which had been inoculated with a few individual colonies of the relevant test germs, at 36° C. After a distinct turbidity had been obtained, sterile nutrient broth was added to the suspensions in such an amount that the turbidity thereof corresponded to McFarland standard 1.0 (approx. 3×10^8 CFU/ml). Test germ suspensions were diluted again 1:10 with sterile broth and the germ count thereof was determined by the surface method using a Spiralometer. The inoculated plates were incubated under the conditions indicated in Table 1 and then evaluated.

Table 1: Inoculation and Incubation of Test Germ *Staphylococcus aureus*

Strain Name	Conditions	Nutrient Medium	Incubation
ATCC6538	Aerobic	Mueller-Hinton	18h at 36°C

As with the examples in the Specification, the MIC (minimum inhibiting concentration, table 2) was regarded as the lowest concentration of active compound at which macroscopically there is no growth. Minimal, barely visible growth or few small individual colonies were evaluated as inhibition.

Determination of Synergy Indices

Synergy Indices (SI) indicated in table 2 were determined in accordance with the Kull et al [1,2] equation

References:

[1] F. C. Kull et al.; Applied Microbiology 9; p. 538-541 (1961)
[2] D. C. Steinberg; Cosmetics & Toiletries 115 (11); p. 59-62 (2000)

Table 2:

Sample: 1,2-hexanediol (C6), 1,2-octanediol (C8) and mixtures thereof	MIC (Minimum Inhibiting Concentration) *Staphylococcus aureus* (ATCC 6538)	Synergy index according to Kull's equation *Staphylococcus aureus* (ATCC 6538)
C6	12500 ppm	Not applicable
C8	3125 ppm	Not applicable
C6 : C8 (1 : 1)	3125 ppm	0.625
C6 : C8 (4 : 1)	6250 ppm	0.800
C6 : C8 (1 : 4)	3125 ppm	0.850
C6 : C8 (10 : 1)	12500 ppm	1.300
C6 : C8 (50 : 1)	12500 ppm	1.060

SI <1 corresponds to a synergistic activity

SI = 1 corresponds neither to a synergistic nor to an antagonistic activity

SI >1 corresponds to an antagonistic activity

Conclusion

The results indicated in table 2 show by way of example a synergistic intensification of the activity of mixtures of 1,2-hexanediol and 1,2-octanediol in ratios of 4:1, 1:1 and 1:4. In these cases, Kull values <1 were calculated indicating synergy. In contrast, in the case of the 10:1 and 50:1 ratios, calculated Kull values were ≥1 indicating no synergism.

8. The synergy of mixtures of 1,2-alkanediols is an unexpected result that was neither disclosed nor suggested by the cited references, whether alone or in combination. The chemical and biological arts are two of the most unpredictable arts. Thus, the fact that a reference discloses an antibacterial synergy between a first 1,2-alkanediol and 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one or sodium capryl lactyl lactylate or glyceryl poly(meth)acrylate, does not have any bearing on whether a mixture of the first 1,2-alkanediol and a second 1,2-alkanediol will produce a similar antibacterial synergy. The structures of 2-hydroxy-4-(1-methylethyl)cyclohepta-2,4,6-trien-1-one, sodium capryl lactyl lactylate and glyceryl poly(meth)acrylate, are simply too different from the claimed 1,2-alkanediols to assume that a second 1,2-alkanediol would interact with the first 1,2-alkanediol and target microbes to produce the same antimicrobial effect (*i.e.*, a synergy). Accordingly, it is my opinion that there is nothing in any of the cited references, whether alone or in combination, that discloses or suggests that the claimed mixture of 1,2-alkanediols would exhibit the claimed synergistic antimicrobial effect as demonstrated by the Kull value.

For the reasons noted above, the claimed antimicrobial compositions are neither anticipated nor rendered obvious by the cited references. In my opinion, the claimed antimicrobial mixtures, which contain the synergistic mixture of 1,2-alkanediols, are quite distinct from any of the cited references and cannot be considered to be known, expected, or suggested based on their respective teachings.

9. I further state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2008 08 07
Date

Dr. Gerhard Schmaus